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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GODDARD, LAURA B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 11/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/613,222	RUBINFELD ET AL.	
	Examiner	Art Unit	
	Laura B. Goddard, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *59-61 and 63-76* is/are pending in the application.

4a) Of the above claim(s) *70-72* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *59-61,63-69 and 73-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892) 7/3/03

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 12/10/03

3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 1/25/06; 11/9/06, 7/17/06, 9/23/05, 8/25/05

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

DETAILED ACTION

1. The Amendment filed September 19, 2006 in response to the Office Action of April 19, 2006, is acknowledged and has been entered. Previously pending claims 59 and 64 have been amended. Claim 62 was canceled. Claims 59-61, 63-69, and 73-76 are currently being examined.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

NEW REJECTION

(based on new considerations)

Claim Rejections - 35 USC § 102

3. Claims 59-61 and 63-65 are rejected under 35 U.S.C. 102(b) as being anticipated by Covey et al (Eur J Cancer Clin Oncol, 1985, 21:109-117).

The claims are drawn to a method for treating a patient having a tumor comprising: intravenously or subcutaneously administering to the patient a therapeutically effective amount of a DNA methylation inhibitor at a dose below 50 mg/m^2 per day (claim 59), wherein the DNA methylation inhibitor is a cytidine analog and is decitabine (claims 60, 61), wherein the DNA methylation inhibitor is decitabine and is administered subcutaneously (claim 63), wherein the decitabine is administered at a dose ranging from about 2 to less than 50 mg/m^2 per day (claim 64), wherein the decitabine is administered at a dose ranging from 5-20 mg/m^2 per day (claim 65).

Covey et al teach a method for treating tumors in patients comprising intravenously administering or subcutaneously administering decitabine (also known as DAC) at a dose below 50 mg/m^2 per day (abstract; Figure 3; Tables 2 and 7). Covey et al teach that decitabine was administered as a single dose of 6.5 mg/kg (this includes 19.60 mg/m^2 which is the equivalent of 6.5mg/kg; see Dose Calculator, Oncology Tools, www.fda.gov/cder/cancer/animalframe.htm, for dosage value of 6.5 mg/kg converted to mg/m^2), which is less than 50 mg/m^2 and between 5 and 20 mg/m^2 (Table 2; p. 113, col. 2).

NEW REJECTION

(necessitated by amendment)

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 64 is rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation wherein "dose ranging from **about 2 to less than 50 mg/m^2 per day**" has no clear support in the specification and the claims as originally filed. THIS IS A NEW MATTER REJECTION.

Applicants amended claim 64 to overcome the 112 2nd rejection of claim 64 in the previous Office Action (p. 3). Applicants do not point to support in the specification for the amendment. A review of the specification reveals support for

a dose ranging from 2-50 mg/m^2 ([00103]). There does not appear to be support for a dose ranging from **about** 2 **to less than** 50mg/m^2 per day. The subject matter claimed in claim 64 broadens the scope of the invention as originally disclosed in the specification.

MAINTAINED REJECTIONS

Claim Rejections - 35 USC § 102

5. **Claims 59-61, 64, 65, 67-69, 75, and 76 remain rejected under 35 U.S.C. 102(b)** as being anticipated by Lenzi et al (International J of Oncology, 1996, 6:447-450). As stated in the previous Office Action pages 4-5:

Lenzi et al. teach a method for treating a patient having a tumor comprising administering to the patient a DNA methylation inhibitor, 2'-deoxy-5-azacytidine (a cytosine analog), in combination with a therapeutically effective amount of an anti-neoplastic agent (cisplatin- a platinum compound) wherein the disease associated with abnormal cell proliferation is a malignant tumor including colorectal, head and neck, non-small cell lung, breast, and pancreatic tumors (page 449, 2nd column). The specification teaches (page 17, line 1) that decitabine is equivalent to 5-aza-2'-deoxycytidine. Thus, for examination purposes it was assumed that the prior art 2 '-deoxy-5-azacytidine was equivalent to 5-aza-2'-deoxycytidine.

Lenzi et al. further teach that decitabine is administered intravenously to the patient per day at a dose below 50 mg/m^2. The dosages of decitabine included 10, 20, 30, 40 and 50mg/m^2 (Table II, page 449). The reference further

teaches that decitabine was administered intravenously over 30 minutes each day for 3 consecutive days followed by the administration of cisplatin on day 4. Thus, the DNA methylation inhibitor was administered prior to the alkylating agent. Additionally, although the reference does not specifically teach that the activity of the administered alkylating agent is "adversely affected by aberrant DNA methylation" (Claim 67), applicant's disclosure clearly includes cisplatin as one of the many anti-neoplastic agents whose activity in vivo is adversely affected by aberrant DNA methylation (page 7, line 24; page 20 lines 5-22).

Claim Rejections - 35 USC § 103

6. **Claims 59-61, 63, 64, 66, and 73-76 remain rejected under 35 U.S.C. 103(a)** as being unpatentable over WO 99/01118 (Atherogenics, Inc., January 1999, IDS) in further view of Lenzi et al. (International Jnl. Oncology, 1995, Vol. 6 (2), pages 447-450). As stated in the previous Office Action, pages 6-9:

WO 99/01118 teaches (page 83, line 5) a method for treating a patient having a tumor comprising administering to the patient a DNA methylation inhibitor (decitabine) wherein the inhibitor is administered intravenously or subcutaneously or in a slow release dosage form (page 48) wherein the tumor is a benign tumor such as a hemangioma (page 46 and 84) or a cancer of the ovaries (page 47 and 85).

WO 99/01118 does not specifically teach that the dosage of the DNA methylation inhibitor (decitabine) is at a dose below 50 mg/m2 (Claim 59), or a dose ranging from 2-50 mg/m^2 (Claim 64).

Through phase I and II trials of a laboratory-derived synergistic combination of cisplatin and 2'-deoxy-5-azacytidine (decitabine) in cancer patients, Lenzi et al. teach that the maximum tolerated dose of decitabine is 50 mg/m2, absent any patient toxicity. However, Lenzi et al. caution that the dosage should be lowered in certain patients that accrue various side effects such as granulocytopenia with infection and thrombocytopenia associated with bleeding or grade 4 non-hematological toxic effects. In such cases, the dosage of decitabine was reduced to 30 mg/m2 (see page 448, 1st column, last paragraph). Further, the reference teaches that dose modification to 40 mg/m^2 was necessary upon hematological toxicity with an AGC of<500 cells/mm^3 or a platelet count of<50,000 cells/mm^3 or if nonhematological toxic effects grade 3 were seen.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to include the administration of decitabine at a dosage below 50 mg/m^2 and or ranging between 2 and 50mg/m^2. One would have been motivated to do so because Lenzi et al. suggest that the maximum tolerated dose (MTD) of decitabine is 50 mg/m^2 absent patient toxicity. However, those of ordinary skill in the art immediately recognize that patient toxicity is often a limiting factor in dose responses and that for some patients the MTD will invoke serious side effects. For example, Lenzi et al. caution that the dosage should be lowered in certain patients that accrue various side effects such as

granulocytopenia with infection and thrombocytopenia associated with bleeding or grade 4 nonhematological toxic effects. In such cases, the dosage of decitabine was reduced to 30 mg/m2 (see page 448, 1st column, last paragraph). Further, Lenzi et al. teach that dose modification to 40 mg/m^2 was necessary upon hematological toxicity with an AGC of<500 cells/mm^3 or a platelet count of<50,000 cells/mm^3 or if non-hematological toxic effects grade 3 were seen. Thus, because one of ordinary skill in the art would not reasonably expect that all patients being treated would safely tolerate decitabine at 50 mg/m^2, one of ordinary skill would successfully reason that a subset of patients must be administered less than the MTD of decitabine.

Double Patenting

7. **Claims 59-61, 63-65, 67-69, and 73-76 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting** as being unpatentable over claims 1-7, 14-17, and 19 of copending **Application No. 10/867621**. Although the conflicting claims are not identical, they are not patentably distinct from each other because the current application is broadly drawn to a method of treating a patient having a tumor comprising administering (intravenously or subcutaneously) to the patient a DNA methylation inhibitor at a dose below 50 mg/m2 wherein the DNA methylation inhibitor is decitabine further comprising administering an alkylating agent which is a platinum compound. These claims are represent an obvious variation from the pending claims drawn to a method of inhibiting a disease associated with abnormal cellular proliferation

comprising administering to a patient a DNA methylation inhibitor at a dose of 1-100mg/m2 in combination with a therapeutically effective amount of a platinum compound. Both set of claims treat the same conditions with the same compounds within the same dosage requirements. Thus, although the claims are not identical, there is no patentable distinction between the two pending claim sets.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments for 102(b) Rejection

8. Applicants argue that Lenzi et al fails to teach or suggest the claimed method of using a therapeutically effective amount of a DNA methylation inhibitor a dose below 50 mg/m^2 per day to treat a patient having a tumor. Applicants argue that there are no objective responses in the patients treated under the dosage conditions employed as stated in Lenzi et al, therefore, Lenzi et al does not teach the claimed method of treating a patient (p. 6-7).

The argument has been considered but is not found persuasive because Lenzi et al teach identical method steps for the claimed method and, hence the method taught by Lenzi et al meets the limitations of a method for treating a patient having a tumor comprising administering to the patient a therapeutically effective amount of decitabine. Applicants believe amendment of claim 59 to recite "therapeutically effective amount" of a DNA methylation inhibitor distinguishes the claimed method form the prior art, however, because the

method steps taught by Kenzi et al are identical to the method steps recited by the claimed method, meaning, the amount of decitabine administered in the method taught by Lenzi et al is the same as in the claimed method, the amount of decitabine administered in the method of Lenzi et al would also be therapeutically effective.

Applicants appear to be arguing that Lenzi et al teaches away from a therapeutically effective amount of DNA methylation inhibitor because the results were to treatment were poor, however, Lenzi et al teaches still anticipated the claimed method. **MPEP 2131.05 states:** A reference is no less anticipatory if, after disclosing the invention, the reference then disparages it. The question whether a reference "teaches away" from the invention is inapplicable to an anticipation analysis. Celeritas Technologies Ltd. v. Rockwell International Corp., 150 F.3d 1354, 1361, 47 USPQ2d 1516, 1522-23 (Fed. Cir. 1998) (The prior art was held to anticipate the claims even though it taught away from the claimed invention. "The fact that a modem with a single carrier data signal is shown to be less than optimal does not vitiate the fact that it is disclosed."). See also Atlas Powder Co. v. IRECO, Inc., 190 F.3d 1342, 1349, 51 USPQ2d 1943, 1948 (Fed. Cir. 1999) (Claimed composition was anticipated by prior art reference that inherently met claim limitation of "sufficient aeration" even though reference taught away from air entrapment or purposeful aeration.). The question whether a reference "teaches away" from the invention is inapplicable to an anticipation analysis.

Response to Arguments for 103(a) Rejection

9. Applicants argue that Lenzi et al fails to teach or suggest the claimed method of using a therapeutically effective amount of DNA methylation inhibitor at a dose below 50 mg/m^2 per for treating a patient having a tumor, thus the cited references each alone or in combination fail to teach all elements of the claims and a *prima facie* case of obviousness has not been established under 35 USC 103(a) (p. 8).

The argument has been considered but has not been found persuasive because the method taught by Lenzi et al anticipates the claimed method for the reasons set forth above in section 8, hence a *prima facie* case of obviousness has been established for the reasons set forth above in section 6.

Response to Arguments for Provisional Double Patenting

10. Applicants argue that the MPEP 804 states that a provisional double patenting rejection in one application should be withdrawn if it is the only rejection remaining in that application (p. 9).

The argument has been considered but is not found persuasive because the provisional rejection of the claims over pending application 10/867,621 is not the only remaining rejection and the claims are not allowable, hence the provisional rejection is maintained.

11. All other rejections recited in the Office Action mailed April 19, 2006 are hereby withdrawn. Applicants submitted a terminal disclaimer to overcome the

double patenting rejection over US Patent 6,613,753. The 102(a) rejection as anticipated by Plumb et al is withdrawn because intraperitoneal (i.p.) injection is not considered to be subcutaneous (s.c) injection by those skilled in the art.

12. **Conclusion:** No claims are allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura B. Goddard, Ph.D. whose telephone number is (571) 272-8788. The examiner can normally be reached on 8:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Laura B Goddard, Ph.D.
Examiner
Art Unit 1642

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER